UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,754	02/02/2007	Jalaj Arora	5999-0525PUS3	2942

54080 7590 08/11/2010

BIRCH, STEWART, KOLASCH & BIRCH, LLP
P.O. BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
COUGHLIN, MATTHEW P	
ART UNIT	PAPER NUMBER
1626	

MAIL DATE	DELIVERY MODE
08/11/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,754	ARORA ET AL.	
	Examiner	Art Unit	
	Matthew P. Coughlin	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,10-16,18-20,25-28 and 30-38* is/are pending in the application.

4a) Of the above claim(s) *4,20 and 32-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,10-16,18,19,25,26,28,30 and 31* is/are rejected.

7)☒ Claim(s) *27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3, 4, 10-16, 18-20, 25-28 and 30-38 are pending in the application. Claims 1, 3, 10-16, 18-19, 25-26, 28 and 30-31 are rejected. Claim 27 is objected to. Claims 4, 20 and 32-38 are withdrawn from further consideration.

Election/Restrictions

The entire scope of the instantly elected Group III within claim 1 has been searched and been found to be free of the prior art. Applicant's claims are still currently drawn (in part) to non-elected subject matter (where X5 is other than a bond).

This application contains claims 4 and 20 drawn to an invention nonelected with traverse in the reply filed on January 15th, 2010. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Response to Amendment / Argument

Objections and rejections made in the previous Office Action that do not appear below have been overcome by Applicant's amendments to the claims. Therefore, arguments pertaining to these rejections will not be addressed.

Applicant has traversed the rejection of claims 1-3, 5-19, 21-26, 28 and 30-31 under 35 USC 112 2nd paragraph based upon the definition of R2 and R3 which have improper valences on the grounds that the skilled artisan would readily understand that the scope of the claims does not encompass compounds having an improper valence. This traversal is not persuasive since the language of the claims explicitly points to compounds that have the improper

valence, i.e. the C_0 moieties. A skilled artisan would not expect the claims to show an improper valence when the improper valence could be easily avoided by an amendment that removes only the improper valences, i.e. amending C_{0-4} to be C_{1-4}. The fact that Applicant clearly provides a limitation to cover improper valences renders the claims indefinite. The rejection is maintained with respect to claims 1, 3, 10-16, 18-19, 25-26, 28 and 30-31 and withdrawn from cancelled claims 2, 5-9, 17 and 21-24.

Applicant has traversed the rejection of claims 28 and 30-31 for lacking enablement for:

(1) a pharmaceutical composition comprising a preventatively effective amount of a compound of formula I,

(2) a compound of formula I for use in therapy, and

(3) a compound of formula I for use in the treatment or prevention of mGluR 5 mediated disorders.

Applicant's traversal is on the grounds that the examiner has not provided sufficient reasons for doubting that there is sufficient enablement for the present invention as claimed. Applicant's traversal is not found persuasive since the instant claims are drawn compound and compositions for use in the prevention of disease for which no guidance is provided and for use the treatment or prevention of mGluR 5 disorders. As discussed in the maintained rejection below. Applicant has not provided guidance as to which compounds may be used to prevent what diseases and in what amount is sufficient to prevent such diseases. Furthermore, Applicant has not provided guidance in how to determine which disease are within the scope of mGluR 5 disorders and furthermore which of these diseases are treatable or preventable using the instant compounds. A person having ordinary skill in the art would have to engage in undue experimentation to determine which, if

any, compounds can be used to prevent diseases and which, if any, diseases can be treated or prevented using the instant compounds. See maintained rejection below.

Maintained Claim Rejections - 35 USC § 112 – 2md paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 10-16, 18-19, 25-26, 28 and 30-31are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation that R2 and R3 can be:

C_{0-4}alkyl(S)C_{0-4}alkyl, C_{1-4}alkyl(SO)C_{0-4}alkyl, C_{1-4}alkyl(SO_2)C_{0-4}alkyl, (SO)C_{0-4}alkyl, (SO_2)C_{0-4}alkyl.

The structure of the above groups is unclear where the alkyl group is C_0. Such groups appear to have an improper valence.

Maintained Claim Rejections - 35 USC § 112 – 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28 and 30-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(1) a compound of formula I, and

(2) a pharmaceutical composition thereof comprising a therapeutically effective, but not preventatively effective, amount of a compound of formula I,

does not reasonably provide enablement for:

(1) a pharmaceutical composition comprising a preventatively effective amount of a compound of formula I,

(2) a compound of formula I for use in therapy, or

(3) a compound of formula I for use in the treatment or prevention of mGluR 5 mediated disorders.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is *undue*. These factors include, but are not limited to: (a) breadth of the claims; (b) nature of the invention; (c) state of the prior art; (d) level of one of ordinary skill in the art; (e) level of predictability in the art; (f) amount of direction provided by the inventor; (g) existence of working examples; and (h) quantity of experimentation needed to make or use the invention based on the content of the disclosure. (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The above factors, regarding the present invention, are summarized as follows:

(a) ***Breadth of the claims*** - The breadth of the claims is drawn to all compounds of formula I and pharmaceutical compositions thereof with intended uses for prevention and treatment of various disorders.

NOTE: "Treatment" and "therapeutically" are defined as including prevention on page 23, lines 20-23 of the specification.

The diseases, disorders, or conditions encompassed by the instant claims include, for example, Alzheimer's disease, pain, stroke, etc.

(b) ***Nature of the invention*** - The nature of the invention is drawn to a compounds and compositions thereof for use in the pharmaceutical treatment and prevention of diseases and disorders.

(c,e) ***State of the prior art*** **and predictability in the art** - The state of the prior art is that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

According to the specification, the instant compounds are antagonists for mGluR 5; however, the prior art has not advanced to the point where a demonstration of activity at mGluR 5 can be extrapolated to the treatment or prevention of "mGluR 5 mediated disorders." There is no teaching the prior art that enables a person having ordinary skill in the art to recognize which diseases or disorders fall within the scope of "mGluR 5 mediates disorders" and would be treatable or preventable using the instant compounds. Bird et al. (Trends in Pharmaceutical Sciences, 30, 2009, 617-623) teach that the mGlu5 receptor is involved in many different pathways and modulating of mGlu5 function will likely affect multiple pathways (page 618). There is no predictability in the art as to how a particular mGlu5 binder will elicit a given response or what that response may be. Instead, the ability to treat or prevent a disease that acts through the mGlu5 receptor requires in depth studies to study the effect of the treatments on the desired pathways and other distinct pathways.

Furthermore, claim 30 is drawn to therapy, in general, and includes the treatment and prevention of various diseases and disorders including cancer. The state of the art with respect to cancer is that despite the common result of uncontrolled cell growth and replication, the various types of cancers have widely varied causes. Luo et al. (Cell, 2009, 136, pages 823-837) teach that (p. 823):

> *[I]t is clear that there is tremendous complexity and heterogeneity in the patterns of mutations in tumors of different origins.*

Accordingly, despite the common phenotypic traits of tumors brought upon by genetic alterations, the underlying causes result in a significant complexity in treating cancer generally. There is no known target that can be activated/inhibited that would be expected to result in the treatment of all types of cancer generally. Furthermore, despite that particular therapies, such as, radiation

and chemotherapy, are used for a variety of cancers, these therapies are still not fully understood. Luo et al. teach that (p. 824):

> *[W]e still do not have a clear molecular understanding of why these agents work to selectively kill tumor cells and, conversely, why they eventually fail.*

Therefore, any claim to the treatment of cancer, in general, requires the support of extensive studies to demonstrate that the particular mode of treatment applies to treating all types of cancer since there is no mode of action that can reliably lead to the treatment of all types of cancer.

(d) ***Level of one of ordinary skill in the art*** - The artisans making and using applicant's pharmaceutical compositions would be a collaborative team of synthetic chemists and/or health practitioners, possessing commensurate degree level and/or skill in the art, as well as several years of professional experience. The level of skill in the art is high; however, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* or *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

(f-g) ***Amount of direction provided by the inventor*** **and existence of working examples** - The only direction or guidance present in the instant specification is the list of diseases and disorders on pages 2-4 of the specification that may be treatable using the instant compounds. There are no working examples present for the treatment or prevention of any disease or disorder by administering the instant compounds.

Test assays and procedures are provided in the specification on pages 81-83 for measuring Group I receptor antagonist activity; however, the disclosure does not provide how the *in vitro* data system correlates to the treatment of the assorted disorders of the instant claims.

Applicant has provided an *in vivo* assay on pages 83-85, which appears to be predictive of the ability to treat, but not prevent, gastro-esophageal reflux disease; however, no data has been presented for this assay and it is not clear if the instant compounds have been studied in this assay.

With respect to Applicant's claim to prevention, there is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the numerous diseases/disorders or conditions claimed herein. That a single compound can be used to treat or prevent all diseases/disorders and conditions embraced by the claim is an incredible finding for which Applicant has not provided supporting evidence. Applicant has not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating or preventing any or all of the diseases/disorders or conditions by administering the instant claimed compound.

Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(h) ***Quantity of experimentation needed to make or use the invention based on the content of the disclosure*** - The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases, disorders, or conditions out of all diseases, disorders, or conditions would be benefited by a compound of formula I and would furthermore then have to determine which of the claimed compounds in the instant invention would provide treatment or prevention of the diseases.

With particular respect to the treatment any type of cancer, as instantly claimed, an undue amount of experimentation is required. Luo et al. teach that the majority of cancer therapies fail when applied generally in that (p. 833):

> *It is very likely that the oncogenes and non-oncogenes to which tumors are addicted will serve as the targets of successful cancer therapies in the future. However, it is already clear that each of even the best therapies applied alone eventually fail in the majority of cases.*

Therefore, the sum of the entire efforts in the field of cancer research has resulted in treatment methods that are not broadly applicable; however, Applicant claims that the instant compounds are the first and only broadly applicable cancer treatment despite the fact that Applicant has merely shown activity in assays where other prior compounds have shown activity and then failed to provide a broad treatment ability.

In fact, Luo et al. teach that even the best individual therapies can only be considered as filters to remove particular subsets of cancer cells with particular properties. Therefore, the most likely broadly applicable cancer treatment will be through a series of treatments with differing targets. Applicant has not provided sufficient teaching in the instant specification to allow a person of ordinary skill in the art to treat all types of cancer using either the instant compounds alone or in an orthogonal therapy approach. Rather, in order to practice the full scope the instant invention, a person of ordinary skill in the art would need to develop a treatment method that has eluded the entire field of cancer research.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue

experimentation. {*In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)}.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

Allowable Subject Matter

Claim 27 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims and amended to remove non-elected subject matter.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Matthew P. Coughlin whose telephone number is (571)270-1311. The examiner can normally be reached on Monday through Thursday from 5:30 am - 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Matthew P. Coughlin/
Examiner, Art Unit 1626

/Rebecca L Anderson/
Primary Examiner, Art Unit 1626